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Original Research Paper

Comprehensive Evaluation of Effectiveness of Nintedanib in the Management of Non-idiopathic Pulmonary Fibrosis: Systematic Review and Meta-analysis

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ABSTRACT:
Introduction: Nintedanib, an intracellular tyrosine kinase inhibitor, has demonstrated potential in inhibiting the progression of lung fibrosis based on preclinical data. Non-Idiopathic pulmonary fibrosis (non-IPF) is caused by a group of diseases with known origin. The aim of this systematic review and meta-analysis was to determine the effectiveness of nintedanib in the management of non-IPF. **Methods**: We gathered studies through the use of databases like Springer, PubMed, Sage journals, Elsevier, ERS publications .IBM SPSS Statistics version 29 was used to evaluate the quality of the studies. It was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The certainty of the evidence was assessed using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach. **Results**: We accumulated 5 studies comprising a total of 6,377 participants (3,187 composed of nintedanib group and the remaining 3190 were the control/comparison group). The results were calculated based on 2 major outcomes. The first outcome was change in FVC percentage from baseline to 12 months which was evaluated using 2 studies. The results observed were a mean of 75.9 %for Baseline FVC and 83.3% at the end of 12 months which clearly showed improvement in the FVC percent for the nintedanib group. The second outcome assessed was rate of decline of FVC in ml/year for 3 studies. The mean reduction rate recorded in the nintedanib group was -93.84 mL/year, which was significantly lower than the corresponding reduction rate of -173.55mL/year reported in the placebo/control group. These differences highlight that nintedanib may slow the progression of non-IPF pulmonary fibrosis. **Conclusion:** Ninetedanib appears to diminish the decline in pulmonary function in various forms of non-IPF and future recommendations should consider Nintedanib for non-IPF. Larger controlled studies in non-IPF are required to be confident about any general effect on mortality by antifibrotic therapy.

Keywords: Non-idiopathic pulmonary fibrosis, Meta-Analysis, Ninetedanib, FVC Rate of decline, FVC percent

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INTRODUCTION:

Non-Idiopathic interstitial pulmonary fibrosis (non-IPF) describes a group of interstitial lung diseases (ILD) that cause inflammation and fibrosis of the lung interstitium, leading to impaired gas exchange due to a known cause. The classic features often include progressive shortness of breath and cough, chest imaging abnormalities, and inflammatory and fibrotic changes in histology. (1) The etiology and most common causes for the development of non-idiopathic pulmonary fibrosis are occupational and environmental exposures to inorganic substances, such as asbestos, beryllium, coal dust, silica, and chromium, which can cause pneumonitis. Post covid 19 pulmonary fibrosis has been one of the major challenges to tackle recently. Other sources include fungi, avian droppings, and bacteria. Drug-induced lung toxicity can result from various drugs, including amiodarone, antineoplastic agents, beta-blockers, methotrexate, nitrofurantoin, statins, and radiation therapy. Connective tissue diseases, such as SLE, sclerosis, and rheumatoid arthritis, can also lead to pulmonary fibrosis. (2) Pulmonary fibrosis of all types is slightly more common in men than women. The overall incidence of ILD of all types is 31.5 per 100,000 in men and 26.1 per 100,000 in women. (3) Patients experience persistent symptoms including cough, breathlessness, and reduced exercise tolerance, accompanied by imaging evidence of lung fibrosis (4). Management typically involves a comprehensive approach incorporating pulmonary rehabilitation, supportive care, and targeted therapies aimed at alleviating symptoms and slowing disease progression (4,7). Notably, in patients with idiopathic pulmonary fibrosis (IPF) and systemic sclerosis-associated interstitial lung disease, treatment with a regimen of 150 mg of nintedanib taken twice daily has shown promise in mitigating the decline of forced vital capacity (FVC) (5). Nintedanib follows linear pharmacokinetics and is metabolized through esterase-mediated hydrolysis and glucuronidation. It is primarily eliminated through the bile/fecal pathway, with minimal renal excretion (6)

The objective of this systematic review and meta-analysis is to contemplate a comprehensive evaluation of the effectiveness of nintedanib in the management of non -idiopathic pulmonary fibrosis which includes post covid 19 pulmonary fibrosis, interstitial lung diseases, systemic sclerosis induced pulmonary fibrosis and many more reasons like autoimmune, hypersensitivity pneumonitis leading to progressive pulmonary fibrosis.

METHODS:

Studies were accumulated by comprehensive search supported by various databases, including Springer, PubMed, Sage Journals, ELSEVIER, ERS publications from the past 5 years (2018-2023). We included interventional studies to keep the meta-analysis precise and excluded all the observational studies, case reports, case studies etc. Due to paucity of the studies on this very subject, we came down to seven papers in which two were excluded as they were under observational studies. Seven authors independently reviewed every study and any discrepancies were settled by consensus. We graded the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Our studies included patients with non-idiopathic pulmonary fibrosis with FVC decline of at least 10% of the predicted value. IBM SPSS 29 was the software used for meta-analysis.

Inclusion Criteria:

1. All studies included patients greater than or equal to 18 years of age.
2. Careful consideration was taken to choose only interventional studies on non idiopathic pulmonary fibrosis which consisted of clinical trials that had Nintedanib as the treatment group and a control / comparison group.
3. A total of 5 interventional studies have been included in this review and analysis paper. 3 of which are compared with the control / placebo group and the other 2 are compared with pirfenidone, thereby allowing a broad spectrum of analysis of the effectiveness of nintedanib in the management of the abovementioned condition.
4. With utmost consideration, only studies which mentioned about non idiopathic pulmonary fibrosis which included conditions like post covid 19 pulmonary fibrosis, systemic sclerosis induced pulmonary fibrosis, interstitial lung diseases, hypersensitivity pneumonitis, autoimmune induced fibrosis etc have only been extensively included.
5. All 5 interventional studies chosen included patients with features of fibrosing lung disease affecting more than 10% of lung volume on

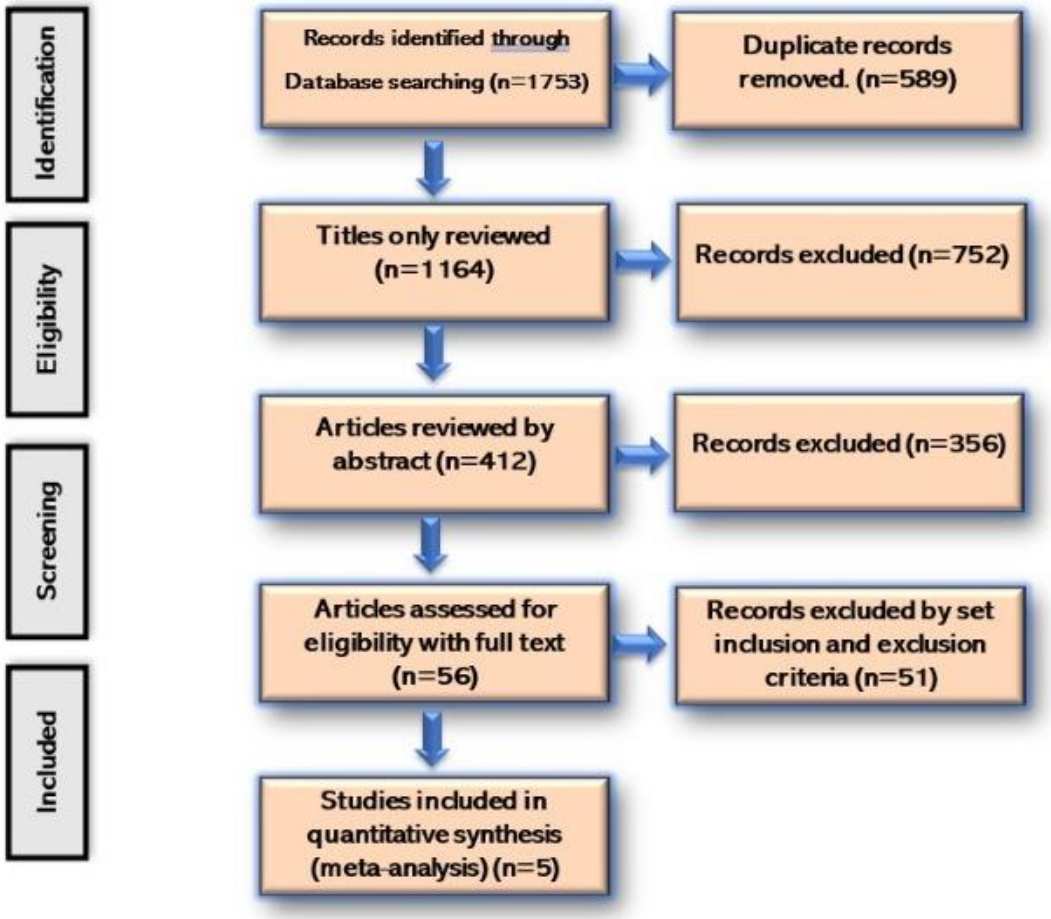
high-resolution CT and a relative decline in the FVC of at least 10% of the predicted .

6. Only those studies comparing the outcome on the basis of FVC has been included.
7. 2 parameters for the specific outcome of FVC have been included:
    a) Rate of decline of FVC in ml/year
    b) Percent of FVC

Exclusion Criteria:

1. All case reports, case studies, literature reviews, meta analysis , observational studies were excluded.
2. All studies excluded pregnant and lactating women.
3. All studies excluded patients who had any kind of contraindications to Pulmonary function tests..
4. Patients with any form of known contraindications to nintedanib (liver cirrhosis , elevated transaminase levels, nintedanib hypersensitivity, high doses of aspirin) were excluded from all studies.
5. Extensive evaluation of studies was done to exclude all those whose outcome was based on measures and variables other than FVC like CT severity score, oxygen saturation etc.

Diagram 1. The Prisma Flow Diagram for systematic review and meta-analysis



RESULTS:

Presented below are the results of the systematic review and meta-analysis examining the effectiveness of nintedanib in the treatment of non-idiopathic pulmonary fibrosis (non-IPF). This study carefully combined data from five selected interventional studies involving a total of 6,377 participants. Of these, 3,187 comprised the nintedanib group, and the remaining 3,190 formed the control/comparison group (Table 1). The primary endpoints assessed were the rate of decline in forced vital capacity (FVC) measured in milliliters per year and change in FVC percentage from baseline to 12 months. Comparative analysis included comparisons of nintedanib with both pirfenidone and control groups. It is noteworthy that the mean age of participants in all studies remained constant at 65.3 years and the

consistent criterion was the presence of non-IPF pulmonary fibrosis in the participant pool (Table 1). The result was primarily based on assessment of 2 specific outcomes; 1) Alteration of FVC percentage in ml from baseline until end of 12 months and 2) Rate of decline in FVC in ml/year.

Table 1, containing studies included, mean age and sample size for overall studies and nintedanib and control/comparison group.

Study	**Mean Age**	**Sample Size**	**Nintedanib Group**	**Control/Comparison Group**
Study 1	65.2	663	332	331
Study 2	78.3	5000	2500	2500
Study 3	68.4	30	15	15
Study 4	54.6	576	288	288
Study 5	68.1	108	52	56
Total	**Mean=65.300**	**Total=6377**	**Total=3187**	**Total=3190**

Conservative representations of forest diagrams and funnel plots were used to increase the robustness of the results. A random-effects model was employed to account for possible heterogeneity within the study pool. Hedges' g was chosen as the preferred effect size metric, allowing comprehensive quantification of the effects of nintedanib on FVC outcomes. Analysis of the first outcome that is alteration of FVC percentage in ml from baseline until 12 months demonstrated a positive trend. Two studies (Study 2 and study 3) were carefully evaluated with the study population of 5000 and 30 out of which 2500 and 15 each in Nintedanib group and pirfenidone comparison group respectively. (**Table 2)**.

Table 2 contains Comparison of FVC percent from baseline and 12 months for Nintedanib and Pirfenidone separately

Study	**Nintedanib (n)**	**Pirefenidone (n)**	**Nintedanib Baseline FVC%**	**Nintedanib 12 months FVC%**	**Pirfenidone Baseline FVC%**	**Pirfenidone 12 months FVC%**
Study 2	2500	2500	80.9 +/- 19.6	84 +/- 13.8	78.7 +/-16.9	83 +/- 17.3
Study 3	15	15	70.9 +/- 18.1	82.6 +/- 20.8	67.2 +/- 13.9	74.4 +/- 19.6
Mean			75.9 %	83.3%	72.95%	78.7%

Study 2 (effect size 0.064, SE 0.0283 , Z=2.258 , 95% CI 0.008- 0.119 and p value = 0.024) with a population of 2500 showed baseline FVC percent for nintedanib group as 80.9 +/- 19.6 and at the end of 12 months it was observed to be 84+/-13.8. **Study 3** (effect size 0.395, SE 0.3692, Z=1.069, 95% CI -0.329- 1.118 and p value = 0.285) with a population of 15 showed baseline FVC percent for nintedanib group as 70.9+/- 18.1 and at the end of 12 months it was observed to be 82 +/- 20.8. (**Fig no 1)**

Fig 1.Effect size estimates, standard error, p value and confidence interval for study 2 and study 3

Effect Size Estimates for Individual Studies

ID	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval Lower	95% Confidence Interval Upper	Weight	Weight (%)
2022	.064	.0283	2.258	.024	.008	.119	1249.362	99.4
2022	.395	.3692	1.069	.285	-.329	1.118	7.335	.6

The overall effect size for both studies is calculated to be 0.066, with a standard error of 0.0282, Z= 2.334 , 95% confidence interval 0.011 - 0.121 and p value sig-2 tailed =0.02. (Fig 2). Overall Chi-square test of homogeneity is 0.798 and p value 0.372 (Fig 3). Heterogeneity measures were evaluated that demonstrated Tau squared heterogeneity 0.000, H squared 1.000 and I squared 0.0%) (Fig 4) . Forest and funnel plots for the same has been shown. (Fig 5 and Fig 6).

Fig 2 shows overall effect size for study 2 and 3,with standard error , p value and confidence interval

Effect Size Estimates

	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval		95% Prediction Interval[a]	
					Lower	Upper	Lower	Upper
Overall	.066	.0282	2.334	.020	.011	.121	.	.

a. Based on t-distribution.

Fig 3. Test of homogeneity for 2 studies

Test of Homogeneity

	Chi-square (Q statistic)	df	Sig.
Overall	.798	1	.372

Fig 4.Test of heterogeneity for 2 studies

Heterogeneity Measures

Overall	Tau-squared	.000
	H-squared	1.000
	I-squared (%)	.0

Fig 5. Forest plot for Study 2 and Study 3 comparing Nintedanib with Pirfenidone on the basis of percent FVC in ml at baseline and after 12 months

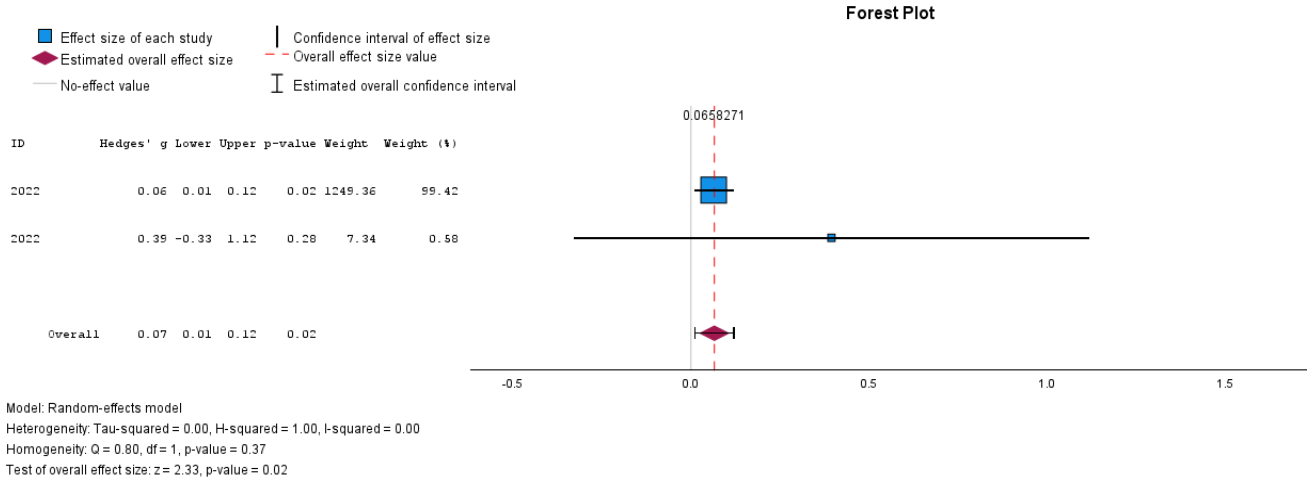
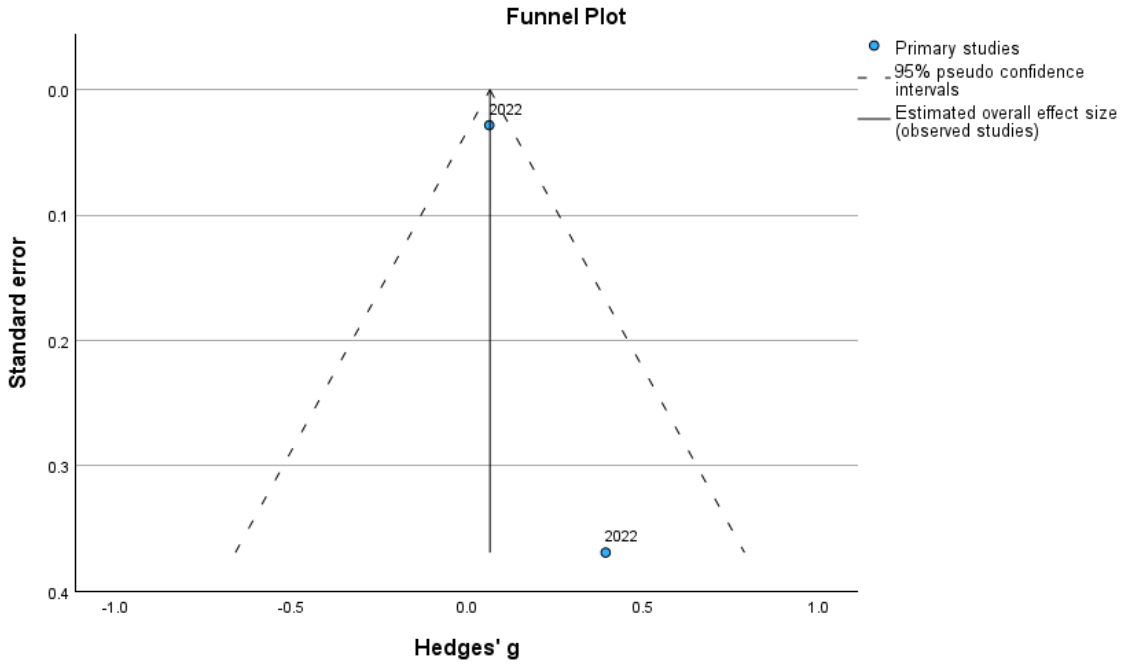


Fig 6. Funnel plot for Study 2 and Study 3 comparing Nintedanib with Pirfenidone on the basis of percent FVC in ml at baseline and after 12 months



Data was analyzed and checked with scrutiny to compare the rate of decline in FVC in ml/year, a key marker of disease progression which confirmed the beneficial effects of nintedanib. Three studies were carefully evaluated with a study population of 663, 576 and 108 out of which 332, 288 and 52 were in the nintedanib group and 331, 288 and 56 were in the control group respectively. (Table 3)

Table 3 showing comparison between Rate of decline of FVC in ml/year between Nintedanib and control group

Study	Nintedanib (n)	Control (n)	Nintedanib Baseline FVC in ml	Control Baseline FVC in ml	Nintedanib Percent predicted value	Control Percent predicted value	Nintedanib Rate of decline FVC ml/year	Control Rate of decline FVC ml/year
Study 1	332	331	2340 +/- 740	2321 +/- 728	68.7 +/- 16.0	69.3 +/- 15.2	- 80.8	-187
Study 4	288	288	2459 +/- 736	2541 +/- 816	72.4 +/- 16.8	72.7 +/- 16.6	-52.4	-93.3
Study 5	52	56	2124	2249	68.1	70.8	-148.31	-240.36
Mean			2307.67 ml	2370.33 ml	69.73	70.93	-93.84 ml/year	-173.55 ml/year

Study 1 (effect size 7.095, SE 0.2103, Z=33.739, 95% CI 6.683-7.507 and p value <0.001). The nintedanib group with a population of 332 showed a rate of decline of FVC of -80.8 ml/ year compared to the control group with a population of 331 showed -187 ml / year. (Table 3)
Study 4 (effect size 2.460, SE 0.2572 , Z=9.564, 95% CI 1.956- 2.964 and p value <0.001) with a population of 288 in nintedanib group showed a rate of decline of FVC of -52.4 ml/year compared to control group with a population of 288 showed -93.3 ml/ year. (Table 3)
Study 5 (effecr size 2.992, SE 0.2103 , Z=33.739, 95% confidence interval 6.683-7.507 and p value <0.001) with a population of 52 in nintedanib group showed a rate of decline of FVC of -148.31 ml/year compared to control group with a population of 288 showed -240.36 ml/ year. (Table 3) Fig 7

Fig 7. Effect size estimates for Studies 1,4 and 5 with standard error, p value and confidence interval.

Effect Size Estimates for Individual Studies

ID	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval		Weight	Weight (%)
					Lower	Upper		
2019	7.095	.2103	33.739	<.001	6.683	7.507	.156	33.3
2019	2.992	.1215	24.621	<.001	2.754	3.230	.156	33.5
2021	2.460	.2572	9.564	<.001	1.956	2.964	.155	33.2

The overall effect size for three studies is calculated to be 4.183, with a standard error of 1.4634 , Z= 2.858, 95% confidence interval 1.314-7.051 and p value 0.004 (Fig 8). Overall Chi-square test of homogeneity is 316.824 and p value <0.01. Heterogeneity measures were evaluated that demonstrated Tau square heterogeneity 6.383, H square 176.327 and I square 99.4% (**Fig 9 and 10) .** Table 3 indicates Studies 1, 4, and 5 comparing nintedanib with placebo or control groups consistently showed a lower rate of FVC decline in the nintedanib-treated group. The mean reduction rate recorded in the nintedanib group was -93.84 mL/year, which was significantly lower than the corresponding reduction rate of -173.55mL/year reported in the placebo/control group(**Table 3**). These differences highlight that nintedanib may slow the progression of non-IPF pulmonary fibrosis. Forest and funnel plots for the same have been shown in Fig 11 and 12.

Fig 8.Overall effect size for 3 studies with standard error, confidence interval and p value

Effect Size Estimates

	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval		95% Prediction Interval[a]	
					Lower	Upper	Lower	Upper
Overall	4.183	1.4634	2.858	.004	1.314	7.051	-32.916	41.281

a. Based on t-distribution.

Fig 9. Test of homogeneity for 3 studies

Test of Homogeneity

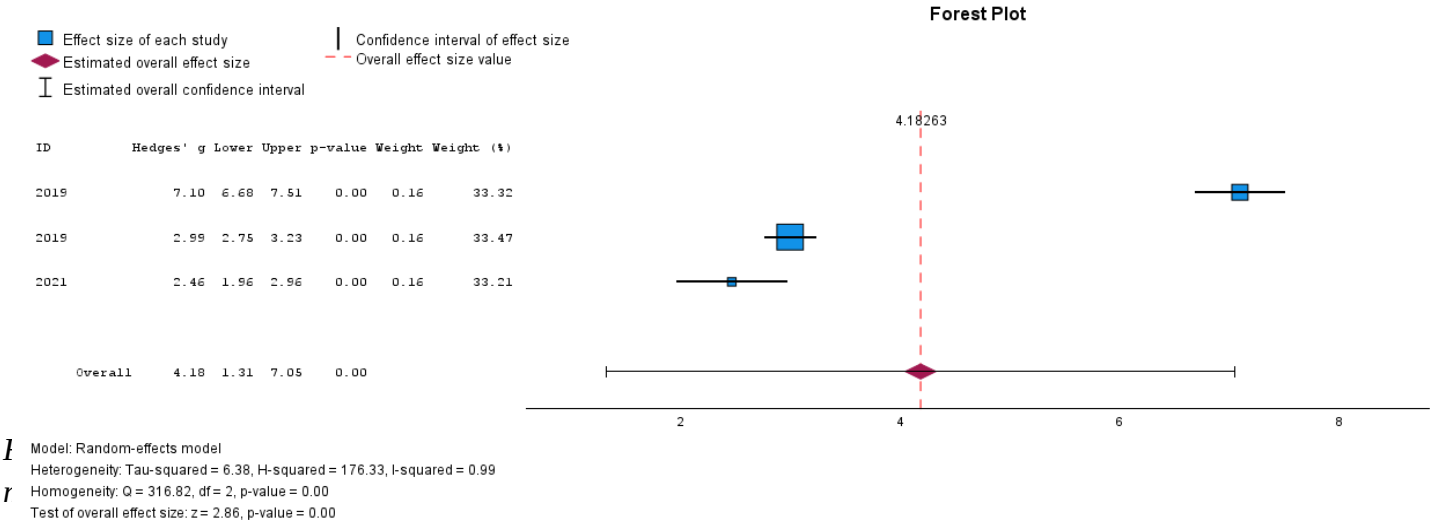
	Chi-square (Q statistic)	df	Sig.
Overall	316.824	2	<.001

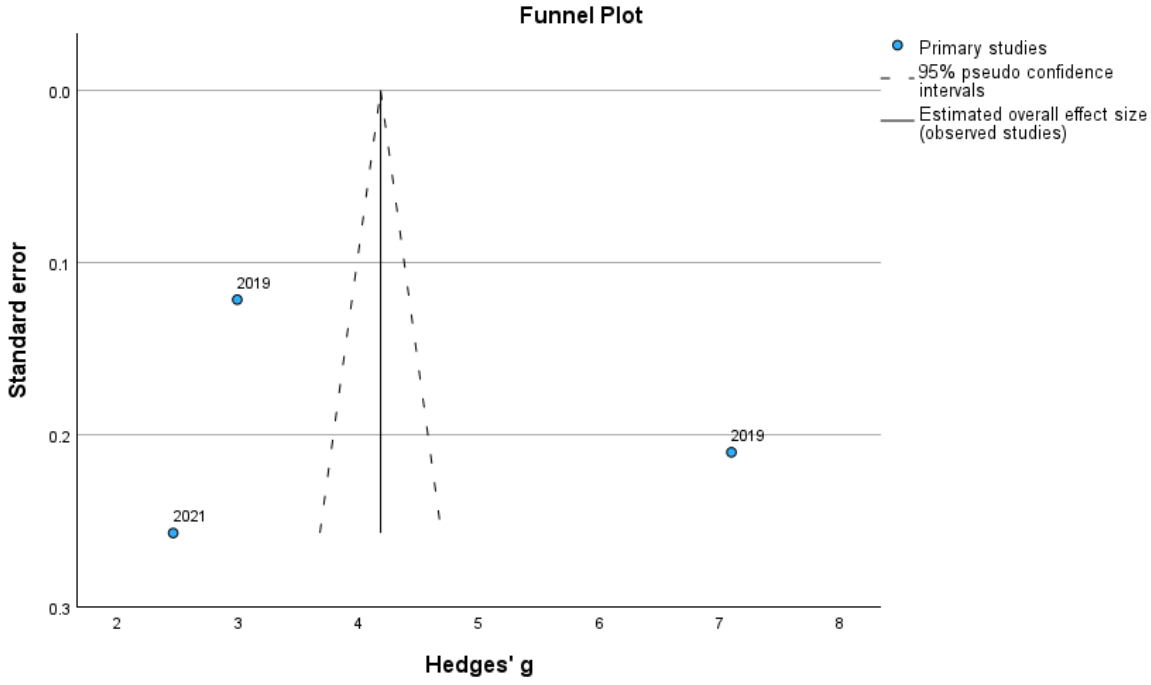
Fig 10. Test of Heterogeneity for 3 studies

Heterogeneity Measures

Overall	Tau-squared	6.383
	H-squared	176.327
	I-squared (%)	99.4

Fig 11 . Forest plot for 3 studies comparing Nintedanib with control group based on Rate of decline in FVC in ml/ year





Adverse Effects:

A key aspect of the overall analysis, a comprehensive assessment of adverse events, found a range of adverse events in subjects receiving nintedanib treatment. These symptoms include various symptoms such as diarrhea, nausea, vomiting, bronchitis, nasopharyngitis, and headache, with diarrhea being the most commonly reported side effect.

Analysis of side effects revealed a significant incidence of diarrhea in people receiving nintedanib. Specifically, of the 3,187 people treated with nintedanib, 1,493 experienced diarrhea, accounting for approximately 68.280 percent of the nintedanib cohort (**Table 4**).

Table 4 containing Studies included, mean age, nintedanib sample size , percentage of patients and number of patients that got diarrhea from nintedanib group.

Study	Sample Size	Nintedanib Group	Diarrhea %	Diarrhea (n)
Study 1	663	332	66.7%	222
Study 2	5000	2500	40%	1000
Study 3	30	15	80%	12
Study 4	576	288	75.7%	218
Study 5	108	52	78.8%	41
Total	**Total=6377**	**Total=3187**	**Mean %= 68.280**	**Total=1493**

This remarkable finding is essential to be interpreted in the broader context of the observed beneficial effects on forced vital capacity (FVC) outcomes. A comprehensive risk-benefit assessment is therefore of paramount importance when considering the appropriateness of a nintedanib intervention for individuals with non-idiopathic pulmonary fibrosis.

This careful review of side effects has revealed a range of symptoms, with diarrhea emerging as a particularly common problem in individuals receiving nintedanib. While the importance of these results is recognized, it is important to contextualize those results in light of the improvements observed in FVC results.

DISCUSSION:

The systematic review and meta-analysis showed an increase in FVC in 12 months in the Nintedanib group and a reduced rate of decline of FVC in mL per year, which depicted that Nintedanib had a beneficial effect in Non Idiopathic Pulmonary Fibrosis population. The overall studies included different Interstitial Lung Diseases subtypes. Study 1 was for a duration of 52 weeks and included Fibrosing Interstitial Lung Disease and King's Brief Interstitial Lung Disease (K-BILD). This study was conducted in 15 countries; Argentina. Belgium, Canada, Chile, China, France, Germany, Italy, Japan, Korea, Poland, Russia, UK, USA, and Spain. Study 2 was done in India and included systemic interstitial lung disease (ILD) progressive fibrosis ILD, diffuse parenchymal lung disorders (DPLDs). Study 3 was conducted by Atatürk University Medical Faculty Hospital for a duration of 12 weeks and included Interstitial Fibrosis and Pulmonary Interstitial Damage. Study 4 Boehringer Ingelheim; SENSCIS Clinical Trial included 32 countries, and included ILD associated with systemic sclerosis. Study 5 is a subgroup analysis that includes Japanese population and the subtypes (K-BILD), Autoimmune ILD, Unclassified ILD, Rheumatoid arthritis associated ILD, Systemic sclerosis associated ILD, MCTD associated ILD. (Table 5)

Table 5. Depicts all studies included in the meta-analysis with the locations, funding , duration , diagnostic criteria , ILD subtypes and study population

Study name	Year	Location	Funding	Duration	PPF Diagnostic Criteria	ILD Subtypes	Study Populations
Study 1 Kevin R. Flaherty, M.D.et al.[6]	2019	15countries: (Argentina. Belgium, Canada, Chile, China, France,	Not funded.	52 weeks	1.Assessment of DLCO. 2. Time to hospitalization. 3. Assessment of PRO questionnaires.	fibrosing interstitial lung disease. King's Brief Interstitial Lung Disease (K-BILD)	663

		Germany, Italy, Japan, Korea, Poland, Russia, UK, USA, and Spain)					
Study 2 Choudhary R, Kumar A, Ali O, et al.[7]	2021	India	Not mentioned.	From May 2021 to April 2022	Inclusion criteria: - age over 18 years. -Patients Tested covid 19 positives -patients with persistent respiratory symptoms -patients with signs of fibrosis or consolidations. Exclusion criteria: -exclude pregnant or lactating women.	systemic interstitial lung disease (ILD) progressive fibrous ILD diffuse parenchymal lung disorders (DPLDs)	5000
Study 3 Buğra Kerget *et al.*[4]	2021	the Atatürk University. Medical Faculty Hospital	Not funded	12 weeks	Inclusion criteria: -age over 18 years. -having fibrosis secondary to covid 19 on radiological imaging. -not requiring intubation and mechanical ventilation during acute covid 19 - being followed up during the 12 weeks (about 3 months) of the study Exclusion criteria: -any conditions that contraindicate PFT. -cognitive disorders -previously or recently detected lung pathology	Interstitial fibrosis pulmonary interstitial damage	30
Study 4 Oliver Distler, M.D.*et al.*,[8]	2019	32 countries Found in	(Boehringer Ingelh	52 weeks	Inclusion criteria: -age above 18 years old	ILD associated with systemic sclerosis.	576

		the protocols	eim; SENSCIS ClinicalTrials.gov number, **NCT02597933. opens in new tab**.)		- patients had systemic sclerosis Exclusion criteria: -patients who had significant pulmonary hypertension -pregnant women		
Study 5 Yoshikazu Inoue.*et al.*, [9]	2021	Japan	Funded.	12 Months	Inclusion and Exclusion criteria.	(K-BILD) Autoimmune ILD Unclassified ILD Rheumatoid arthritis associated ILD. Systemic sclerosis associated ILD MCTD associated ILD	108

Anti-inflammatory treatment was used widely in non-IPF studies, it varied markedly between studies. Although anti-inflammatory treatment is administered frequently in non-IPF lung disease, the evidence of its efficacy/harm in progressive non-IPF is still variable [10,11,12]. A comprehensive assessment of adverse events was made in subjects receiving Nintedanib Treatment. They included symptoms such as diarrhea, nausea, vomiting, bronchitis, nasopharyngitis, and headache, with diarrhea being the most commonly reported adverse effect.

Limitations that apply to the meta-analysis were that study 3 had a small population size. All five studies are interventional study, as there was paucity of studies, one out of the five studies was a subgroup analysis of one of main studies that is included in the meta-analysis.

CONCLUSION:

Nintedanib has shown promise in reducing lung function decline for non idiopathic pulmonary fibrosis. This suggests that future medical guidelines and recommendations should consider inclusion of nintedanib and other antifibrotic agents as a possible treatment option for patients without IPF. However, to establish a more robust and comprehensive understanding of its impact on mortality and overall efficacy, larger controlled studies, with a particular focus on populations with non idiopathic pulmonary fibrosis is required. These studies will help healthcare professionals make more informed decisions about the use of antifibrotic therapy such as nintedanib, which has the potential to improve prognosis and quality of life for patients with such conditions.

Abbreviations:

CI: Confidence interval (95% unless otherwise stated); SE: Standard Error, **FVC**: Forced vital capacity; **IPF**: Idiopathic pulmonary fibrosis; **Non-IPF**: Pulmonary disease with progressive fibrosis not classified as **IPF**, **RCT**: Randomized controlled trial.

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